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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND  
SALES hereby certify that annexed is a true copy of the Provisional specification  
in connection with Application No. 2002951995 for a patent by ALCHEMIA  
PTY LTD as filed on 11 October 2002.



WITNESS my hand this  
Twenty-third day of October 2003

A handwritten signature in cursive script, reading "J. Billingsley".

JULIE BILLINGSLEY  
TEAM LEADER EXAMINATION  
SUPPORT AND SALES

## **CLASSES OF COMPOUNDS THAT INTERACT WITH GPCRs**

### **FIELD OF THE INVENTION**

5 The invention provides classes of biologically active compounds that interact in a pharmaceutically significant manner with G-Protein Coupled Receptors (GPCRs), pharmaceutical compositions containing such compounds and methods of treatment of humans suffering from a disorder which can be at least partially overcome by the compounds or compositions.

### **BACKGROUND OF THE INVENTION**

10 The drug discovery landscape has been transformed by the genomics revolution. Advances in the understanding of biomolecular pathways and the roles they play in disease will lead to vast numbers of targets for therapeutic intervention. GPCRs represent the most important collection of therapeutic  
15 targets available.

GPCRs are proteins that transduce signals across a cell membrane. They consist of a single polypeptide chain that threads back and forth seven times across the phospholipid bilayer that forms the cell membrane. The polypeptide chain has a portion inside the cell which form a G-protein  
20 coupling domain, and a receptor portion outside or in the cell wall. A signal molecule interacts with the receptor which sends the signal through the membrane wall and the signal causes the G-protein coupling domain to interact with a G protein.

Over 50% of marketed drugs target GPCRs. Whilst the druggable  
25 extent of GPCRs numbers some 450 receptors only some 200 GPCRs have been matched with their ligands. Orphan receptors suitable for drug targeting may therefore number in excess of 200 receptors. These are receptors with less than approximately 45% sequence identity to known GPCRs for which ligands have not been identified.

30 The targets of current GPCR drugs include, pain and inflammation, cancer, metabolic and gastrointestinal, cardiovascular and central nervous system disorders.

There is a continuing demand for new therapeutics, especially as our

understanding of biological processes expands from the genomics revolution. The aforementioned GPCRs are suitable targets for therapeutic intervention due to their roles in such disorders as cancers, obesity and erectile dysfunction.

5        Considering the rate of generation and nature of the targets currently being deconvoluted by biologists, there is a need for the development of drug candidates, designed in a rational manner to purposely interact with selected targets, such as the GPCRs.

10        From a drug discovery perspective, carbohydrate pyranose and furanose rings and their derivatives are well suited as templates. Each sugar represents a three-dimensional scaffold to which a variety of substituents can be attached, usually *via* a scaffold hydroxyl group, although occasionally a scaffold carboxyl or amino group may be present for substitution. By varying the substituents, their relative position on the sugar scaffold, and the type of  
15        sugar to which the substituents are coupled, numerous highly diverse structures are obtainable.

      An important feature to note with carbohydrates, is that molecular diversity is achieved not only in the type of substituents, but also in the three dimensional presentation. The different stereoisomers of carbohydrates that  
20        occur naturally or non-naturally, offer the inherent structural advantage of providing alternative, rigid presentation of substituents, to a target's binding site.

      GPCR's are known to bind to peptide ligands. Amino acid side chains and isosteres thereof, can be coupled to different sugar cores in a variety of  
25        alternate, yet fixed presentations. Consequently, by exploiting the numerous monosaccharide stereoisomers available, the conformally fixed nature of the pyranose ring, and the ability to employ a range of substituents, enhanced affinity and selectivity can be tuned for particular targets.

      Employing a related methodology, Hirschmann *et al* (Hirschmann, R.,  
30        *et. al.*, *J. Am. Chem. Soc.*, 1992, 114, 9217-9218, US 5,552,534, WO 97/28172, WO 95/11686) synthesised several compounds designed as somatostatin analogues and integrin binders. The methodology employed by Hirschmann relied on protracted, linear, non-combinatorial syntheses,

employed exclusively non-aminated pyranoses, and did not exploit any epimerisation chemistry to allow greater access to structural diversity. Consequently, these compounds and methods are manifestly distinct from this present invention.

5        We have developed a system that allows the chemical synthesis of highly structurally and functionally diverse derivatised carbohydrate and tetrahydropyran structures, of both natural and unnatural origin. The diversity accessible is particularly augmented by the juxtaposition of both structural and functional aspects of the molecules.

10        Using the axioms of this drug discovery methodology, we synthesised several novel classes of chemotypes in an effort to develop drug candidates against GPCR targets.

#### SUMMARY OF THE INVENTION

15        It is a general object of the invention to provide compounds that interact with GPCRs in a biologically significant manner,

It is a further object of the invention to provide a pharmaceutical formulation comprising at least one compound as described herein or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

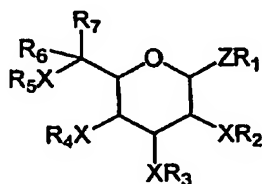
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It is a further object of the invention to provide a method of treatment of a human or animal subject which method comprises administering to the human or animal subject an effective amount of a compound as described herein or a pharmaceutically acceptable salt thereof.

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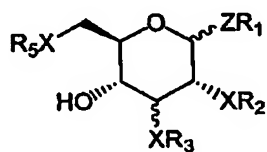
It is a further object of the invention to prepare novel compounds per se.

30        In one aspect the invention provides for compounds of general formula I, that interact with GPCRs in a biologically significant manner,



### General Formula I

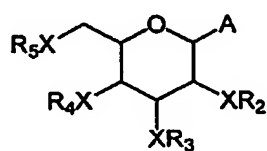
- 5    Wherein the ring may be of any configuration;  
      Z is sulphur, oxygen, CH<sub>2</sub>, C(O), C(O)HNR<sup>A</sup>, NH, NR<sup>A</sup> or hydrogen, in the  
      case where Z is hydrogen then R<sub>1</sub> is not present, R<sup>A</sup> is selected from the set  
      defined for R<sub>1</sub> to R<sub>5</sub>,  
      X is oxygen or nitrogen providing that at least one X of General Formula I is  
 10    nitrogen, alternatively X can be an azide, in which case R<sub>1</sub> to R<sub>5</sub> are not  
      present.  
      R<sub>1</sub> to R<sub>5</sub> are independently selected from the following definition which  
      includes but is not limited to H or an alkyl, acyl, alkenyl, alkynyl, heteroalkyl,  
      aryl, heteroaryl, arylalkyl or heteroarylalkyl substituent of 1 to 20 atoms, which  
 15    is optionally substituted, and can be branched or linear. Typical substituents  
      include but are not limited to OH, NO, NO<sub>2</sub>, NH<sub>2</sub>, N<sub>3</sub>, halogen, CF<sub>3</sub>, CHF<sub>2</sub>,  
      CH<sub>2</sub>F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid,  
      carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl,  
      heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl,  
 20    substituted or unsubstituted imine, sulfate, sulfonamide, phosphate,  
      phosphoramidate, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy,  
      aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl,  
      which may optionally be further substituted, and  
      R<sub>6</sub> and R<sub>7</sub> are hydrogen, or may combine to form a carbonyl function.  
 25    In one embodiment the invention provides for compounds of general formula  
      II that interact with GPCRs in a biologically significant manner,



General Formula II

5    Wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $Z$  and  $X$  are defined as in General Formula I.

In a second embodiment the invention provides for compounds of general formula III that interact with GPCRs in a biologically significant manner,



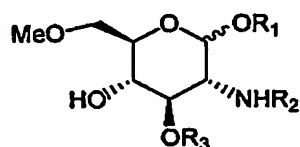
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General Formula III

15    Wherein  $A$  is defined as hydrogen,  $SR_1$ , or  $OR_1$  where  $R_1$  is defined as in General Formula I, and  
 $X$  and  $R_2$  to  $R_5$  are defined as in General Formula I.

In a preferred embodiment the invention provides for compounds of General Formula IV that interact with GPCRs in a biologically significant manner,

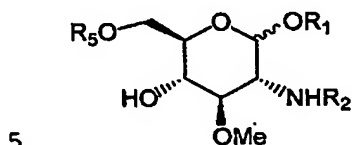
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General Formula IV

25    Wherein  $R_1$ - $R_3$  are defined as in General Formula I.

In a second preferred embodiment the invention provides for compounds of General Formula V that interact with GPCRs in a biologically significant manner,

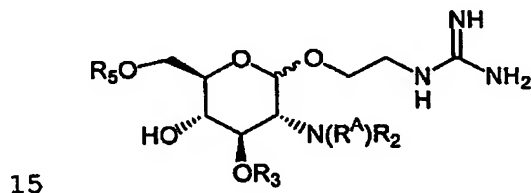


General Formula V

Wherein  $R_1$ ,  $R_2$  and  $R_5$  are defined as in General Formula I.

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In a third preferred embodiment the invention provides for compounds of General Formula VI that interact with GPCRs in a biologically significant manner,



General Formula VI

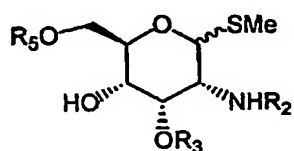
Wherein  $R^A$  is H or combines with  $R_2$  to form an azide, and

20

$R_3$ ,  $R_4$  and  $R_5$  are defined as in General Formula I.

In a fourth preferred embodiment the invention provides for compounds of General Formula VII that interact with GPCRs in a biologically significant manner of,

25

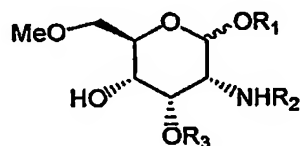


General Formula VII

- 5    Wherein,  $R_2$ ,  $R_3$  and  $R_5$  are defined as in General Formula I.

In a fifth preferred embodiment the invention provides for compounds of General Formula VIII that interact with GPCRs in a biologically significant manner,

10

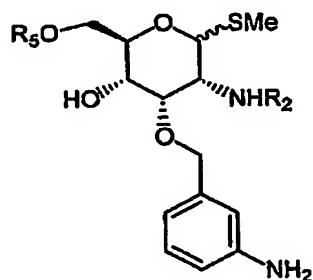


General Formula VIII

- 15    Wherein  $R_1$  to  $R_3$  are defined as in General Formula I.

In a sixth preferred embodiment the invention provides for compounds of General Formula IX that interact with GPCRs in a biologically significant manner,

20

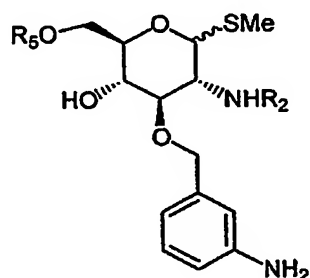


General Formula IX



Wherein  $R_2$  and  $R_5$  are defined as in General Formula I.

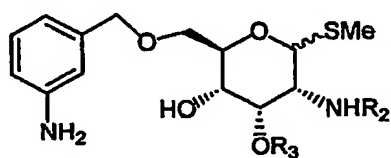
- 5 In a seventh preferred embodiment the invention provides for compounds of General Formula X that interact with GPCRs in a biologically significant manner,



10 General Formula X

Wherein  $R_2$  and  $R_5$  are defined as in General Formula I.

- 15 In an eighth preferred embodiment the invention provides for compounds of General Formula XI that interact with GPCRs in a biologically significant manner,

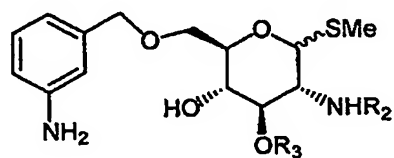


20 General Formula XI

Wherein  $R_2$  and  $R_3$  are defined as in General Formula I.

- 25 In a ninth preferred embodiment the invention provides for compounds of General Formula XII that interact with GPCRs in a biologically significant

manner,



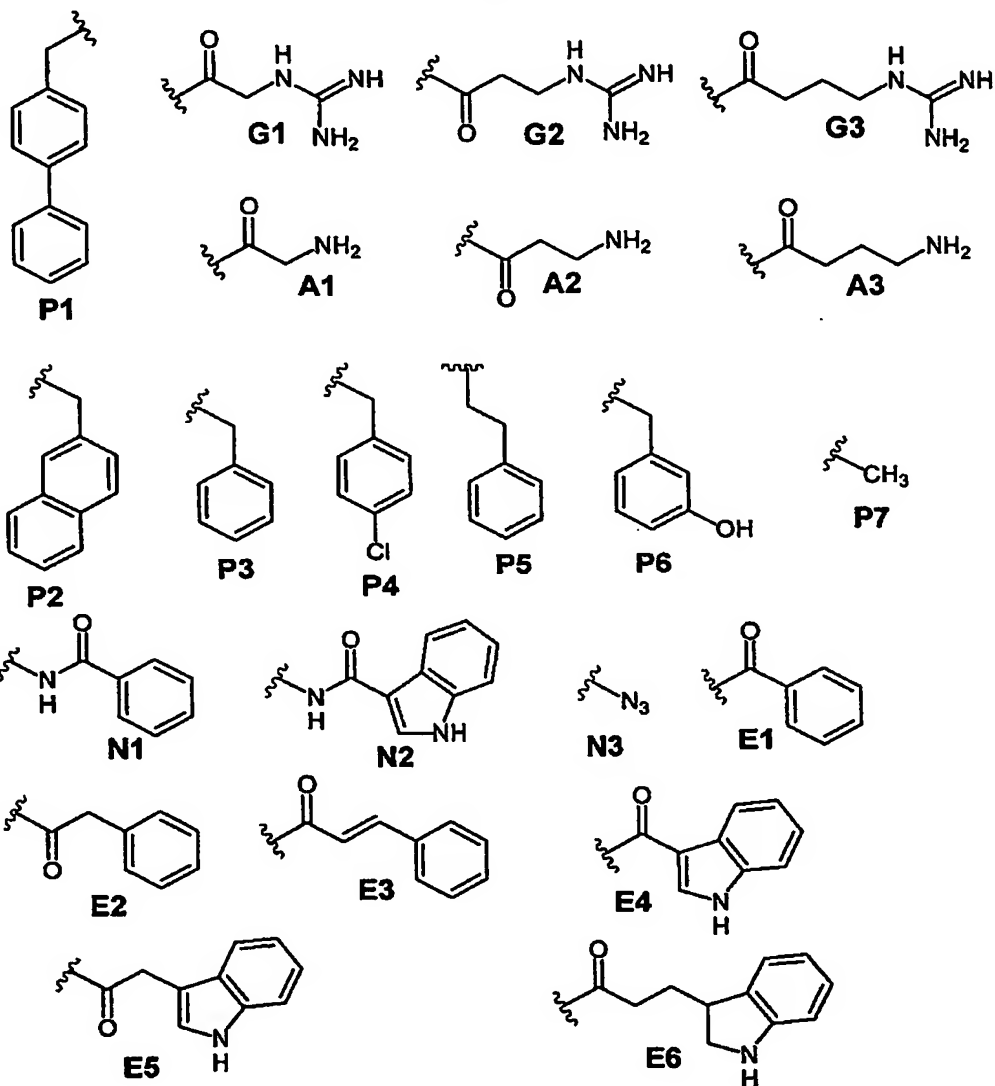
5 General Formula XII

Wherein R<sub>2</sub> and R<sub>3</sub> are defined as in General Formula I.

Examples of the Invention

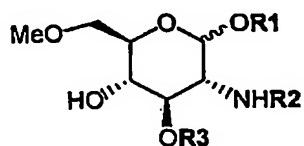
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Substituents per Example Libraries 1-9



### Key

- X1 refers to the MC4 receptor assay, X2 refers to the SST5 receptor assay,  
 5 X3 refer to the CXCR4 receptor assay, and X4 refers to the noradrenalin receptor assay.
- A "++" refers to greater than 75% inhibition at 10 micromolar, a "+" refers to greater than 50% inhibition at 10 micromolar and a "-" is considered inactive.

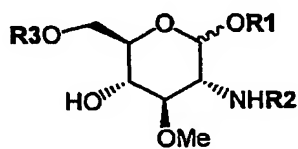
Example Library 1

| Comp. No. | R1 | R2 | R3 | X1 | X2 | c LogP <sub>v</sub> |
|-----------|----|----|----|----|----|---------------------|
| 1         | P1 | G1 | P1 | +  | -  | 3.56                |
| 2         | P1 | G2 | P1 | -  | -  | 3.65                |
| 3         | P1 | G1 | P2 | -  | -  | 2.98                |
| 4         | P1 | G2 | P2 | -  | +  | 3.07                |
| 5         | P1 | G1 | P3 | -  | -  | 1.80                |
| 6         | P1 | A3 | P3 | -  | -  | 2.91                |
| 7         | P1 | G1 | P4 | -  | -  | 2.44                |
| 8         | P2 | G1 | P3 | -  | -  | 1.21                |
| 9         | P2 | A3 | P3 | -  | +  | 2.32                |
| 10        | P2 | G1 | P4 | -  | -  | 1.86                |
| 11        | P3 | G1 | P1 | -  | -  | 1.80                |
| 12        | P3 | G2 | P1 | -  | +  | 1.89                |
| 13        | P3 | A3 | P1 | -  | +  | 2.91                |
| 14        | P3 | G3 | P1 | -  | +  | 2.38                |
| 15        | P3 | G1 | P2 | -  | -  | 1.21                |
| 16        | P3 | G2 | P2 | -  | -  | 1.30                |
| 17        | P3 | G1 | P3 | -  | -  | 0.04                |
| 18        | P3 | G2 | P3 | -  | -  | 0.13                |
| 19        | P3 | A3 | P3 | -  | +  | 1.14                |
| 20        | P3 | G3 | P3 | -  | -  | 0.62                |
| 21        | P3 | G1 | P4 | -  | -  | 0.68                |
| 22        | P3 | G2 | P4 | -  | -  | 0.77                |
| 23        | P3 | A3 | P4 | -  | +  | 1.79                |
| 24        | P3 | G3 | P4 | -  | -  | 1.26                |
| 25        | P4 | G1 | P1 | -  | -  | 2.44                |
| 26        | P4 | G2 | P1 | +  | +  | 2.53                |
| 27        | P4 | G2 | P2 | +  | -  | 1.95                |
| 28        | P4 | G3 | P2 | -  | +  | 2.44                |
| 29        | P4 | G1 | P3 | -  | -  | 0.68                |
| 30        | P4 | G2 | P3 | -  | -  | 0.77                |
| 31        | P4 | A3 | P3 | -  | +  | 1.79                |
| 32        | P4 | G1 | P4 | -  | -  | 1.32                |
| 33        | P4 | G2 | P4 | -  | +  | 1.42                |
| 34        | P4 | G3 | P4 | -  | +  | 1.91                |
| 35        | P5 | G1 | P1 | +  | -  | 2.29                |
| 36        | P5 | G2 | P1 | -  | -  | 2.38                |

|    |    |    |    |    |    |       |
|----|----|----|----|----|----|-------|
| 37 | P5 | G1 | P3 | -  | -  | 0.53  |
| 38 | P5 | G1 | P4 | -  | -  | 1.17  |
| 39 | P1 | G2 | P6 | -  | -  | 1.41  |
| 40 | P5 | G2 | P6 | -  | -  | 0.14  |
| 41 | P6 | G1 | P1 | -  | -  | 1.32  |
| 42 | P6 | G2 | P1 | -  | -  | 1.41  |
| 43 | P6 | G3 | P1 | -  | -  | 1.90  |
| 44 | P6 | G1 | P2 | -  | -  | 0.73  |
| 45 | P6 | G3 | P2 | -  | -  | 1.31  |
| 46 | P6 | G1 | P3 | -  | -  | -0.45 |
| 47 | P6 | G2 | P3 | -  | -  | -0.35 |
| 48 | P6 | G3 | P3 | -  | -  | 0.14  |
| 49 | P6 | G1 | P4 | -  | -  | 0.20  |
| 50 | P1 | G1 | P6 | -  | -  | 1.32  |
| 51 | P1 | A3 | P6 | -  | -  | 2.43  |
| 52 | P1 | G3 | P6 | -  | -  | 1.90  |
| 53 | P2 | G1 | P6 | -  | -  | 0.73  |
| 54 | P2 | G2 | P6 | -  | -  | 0.82  |
| 55 | P2 | A3 | P6 | -  | +  | 1.84  |
| 56 | P2 | G3 | P6 | -  | +  | 1.31  |
| 57 | P3 | A3 | P6 | -  | -  | 0.66  |
| 58 | P3 | G3 | P6 | -  | -  | 0.14  |
| 59 | P4 | G1 | P6 | -  | -  | 0.20  |
| 60 | P4 | G2 | P6 | -  | -  | 0.29  |
| 61 | P4 | A3 | P6 | -  | +  | 1.31  |
| 62 | P4 | A3 | P6 | -  | -  | 0.78  |
| 63 | P5 | A3 | P6 | -  | -  | 1.15  |
| 64 | P5 | G3 | P6 | -  | -  | 0.63  |
| 65 | P6 | A3 | P1 | -  | -  | 2.43  |
| 66 | P6 | A3 | P3 | -  | -  | 0.66  |
| 67 | P6 | G2 | P4 | -  | -  | 0.29  |
| 68 | P6 | A3 | P4 | -  | -  | 1.31  |
| 69 | P6 | G3 | P4 | -  | -  | 0.78  |
| 70 | P1 | A3 | P1 | -  | +  | 4.67  |
| 71 | P1 | G3 | P1 | ++ | -  | 4.14  |
| 72 | P1 | G3 | P2 | -  | +  | 3.56  |
| 73 | P1 | G2 | P3 | -  | +  | 1.89  |
| 74 | P1 | G3 | P3 | -  | -  | 2.38  |
| 75 | P1 | G2 | P4 | -  | +  | 2.53  |
| 76 | P1 | A3 | P4 | -  | +  | 3.55  |
| 77 | P1 | G3 | P4 | +  | +  | 3.03  |
| 78 | P2 | G1 | P1 | +  | +  | 2.98  |
| 79 | P2 | G2 | P1 | +  | +  | 3.07  |
| 80 | P2 | A3 | P1 | -  | ++ | 4.08  |
| 81 | P2 | G1 | P2 | -  | -  | 2.39  |
| 82 | P2 | G2 | P2 | +  | +  | 2.48  |

|     |    |    |    |    |    |      |
|-----|----|----|----|----|----|------|
| 83  | P2 | A3 | P2 | +  | ++ | 3.49 |
| 84  | P2 | G3 | P2 | ++ | +  | 2.97 |
| 85  | P2 | G2 | P3 | -  | -  | 1.30 |
| 86  | P2 | G3 | P3 | -  | +  | 1.79 |
| 87  | P2 | A3 | P4 | -  | ++ | 2.96 |
| 88  | P2 | G3 | P4 | -  | ++ | 2.44 |
| 89  | P4 | A3 | P1 | -  | ++ | 3.55 |
| 90  | P4 | G3 | P1 | +  | +  | 3.03 |
| 91  | P4 | G1 | P2 | -  | -  | 1.86 |
| 92  | P4 | A3 | P2 | -  | ++ | 2.96 |
| 93  | P4 | G3 | P3 | -  | -  | 1.26 |
| 94  | P5 | A3 | P1 | -  | +  | 3.40 |
| 95  | P5 | G3 | P1 | -  | +  | 2.87 |
| 96  | P5 | G1 | P2 | -  | -  | 1.70 |
| 97  | P5 | G2 | P2 | -  | -  | 1.79 |
| 98  | P5 | A3 | P2 | -  | ++ | 2.81 |
| 99  | P5 | G3 | P2 | -  | -  | 2.28 |
| 100 | P5 | G2 | P3 | -  | -  | 0.62 |
| 101 | P5 | A3 | P3 | -  | -  | 1.63 |
| 102 | P5 | G3 | P3 | -  | -  | 1.11 |
| 103 | P5 | G2 | P4 | -  | -  | 1.26 |
| 104 | P5 | A3 | P4 | -  | +  | 2.28 |
| 105 | P5 | G3 | P4 | -  | +  | 1.75 |
| 106 | P1 | A3 | P2 | -  | ++ | 4.08 |
| 107 | P3 | A3 | P2 | -  | ++ | 2.32 |
| 108 | P4 | A3 | P4 | -  | ++ | 2.43 |

## Example Library 2

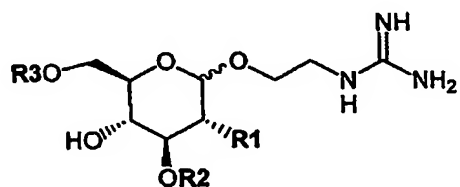


| Comp. No. | R1 | R2 | R3 | X1 | X2 | c LogP |
|-----------|----|----|----|----|----|--------|
| 109       | P1 | G1 | P1 | ++ | -  | 3.56   |
| 110       | P1 | G2 | P1 | +  | -  | 3.65   |
| 111       | P1 | A3 | P1 | -  | -  | 4.67   |
| 112       | P1 | G3 | P1 | +  | -  | 4.14   |
| 113       | P1 | G1 | P2 | +  | -  | 2.98   |
| 114       | P1 | G2 | P2 | -  | -  | 3.07   |
| 115       | P1 | A3 | P2 | ++ | ++ | 4.08   |
| 116       | P1 | G3 | P2 | -  | -  | 3.56   |
| 117       | P1 | G1 | P3 | -  | -  | 1.80   |
| 118       | P1 | G2 | P3 | -  | -  | 1.89   |
| 119       | P1 | A3 | P3 | -  | -  | 2.91   |
| 120       | P1 | G3 | P3 | -  | -  | 2.38   |
| 121       | P1 | G1 | P4 | +  | -  | 2.44   |
| 122       | P1 | G2 | P4 | +  | -  | 2.53   |
| 123       | P1 | A3 | P4 | -  | -  | 3.55   |
| 124       | P1 | G3 | P4 | +  | -  | 3.03   |
| 125       | P2 | G1 | P1 | +  | -  | 2.98   |
| 126       | P2 | G2 | P1 | +  | -  | 3.07   |
| 127       | P2 | A3 | P1 | +  | -  | 4.08   |
| 128       | P2 | G3 | P1 | +  | -  | 3.56   |
| 129       | P2 | G1 | P2 | +  | -  | 2.39   |
| 130       | P2 | G2 | P2 | +  | -  | 2.48   |
| 131       | P2 | A3 | P2 | -  | +  | 3.49   |
| 132       | P2 | G3 | P2 | -  | -  | 2.97   |
| 133       | P2 | G1 | P3 | -  | -  | 1.21   |
| 134       | P2 | G2 | P3 | -  | -  | 1.30   |
| 135       | P2 | A3 | P3 | -  | -  | 2.32   |
| 136       | P2 | G3 | P3 | -  | -  | 1.79   |
| 137       | P2 | G1 | P4 | +  | -  | 1.86   |
| 138       | P2 | G2 | P4 | -  | -  | 1.95   |
| 139       | P2 | A3 | P4 | -  | +  | 2.96   |
| 140       | P2 | G3 | P4 | +  | -  | 2.44   |
| 141       | P3 | G1 | P1 | -  | -  | 1.80   |
| 142       | P3 | G2 | P1 | -  | -  | 1.89   |
| 143       | P3 | A3 | P1 | -  | -  | 2.91   |
| 144       | P3 | G3 | P1 | -  | -  | 2.38   |
| 145       | P3 | G1 | P2 | -  | +  | 1.21   |

|     |    |    |    |    |    |      |
|-----|----|----|----|----|----|------|
| 146 | P3 | G2 | P2 | -  | -  | 1.30 |
| 147 | P3 | A3 | P2 | -  | -  | 2.32 |
| 148 | P3 | G3 | P2 | -  | -  | 1.79 |
| 149 | P3 | G1 | P3 | -  | -  | 0.04 |
| 150 | P3 | G2 | P3 | -  | -  | 0.13 |
| 151 | P3 | A3 | P3 | -  | -  | 1.14 |
| 152 | P3 | G3 | P3 | -  | -  | 0.62 |
| 153 | P3 | G1 | P4 | -  | -  | 0.68 |
| 154 | P3 | G2 | P4 | -  | -  | 0.77 |
| 155 | P3 | A3 | P4 | -  | +  | 1.79 |
| 156 | P3 | G3 | P4 | -  | -  | 1.26 |
| 157 | P4 | G1 | P1 | +  | -  | 2.44 |
| 158 | P4 | G2 | P1 | +  | -  | 2.53 |
| 159 | P4 | A3 | P1 | -  | +  | 3.55 |
| 160 | P4 | G3 | P1 | +  | -  | 3.03 |
| 161 | P4 | G1 | P2 | ++ | +  | 1.86 |
| 162 | P4 | G2 | P2 | ++ | +  | 1.95 |
| 163 | P4 | A3 | P2 | ++ | ++ | 2.96 |
| 164 | P4 | G3 | P2 | +  | -  | 2.44 |
| 165 | P4 | G1 | P3 | -  | -  | 0.68 |
| 166 | P4 | G2 | P3 | -  | -  | 0.77 |
| 167 | P4 | A3 | P3 | -  | +  | 1.79 |
| 168 | P4 | G3 | P3 | -  | -  | 1.26 |
| 169 | P4 | G1 | P4 | -  | -  | 1.32 |
| 170 | P4 | G2 | P4 | +  | -  | 1.42 |
| 171 | P4 | A3 | P4 | -  | +  | 2.43 |
| 172 | P4 | G3 | P4 | +  | -  | 1.91 |
| 173 | P5 | G1 | P1 | +  | -  | 2.29 |
| 174 | P5 | G2 | P1 | +  | -  | 2.38 |
| 175 | P5 | A3 | P1 | +  | +  | 3.40 |
| 176 | P5 | G3 | P1 | +  | -  | 2.87 |
| 177 | P5 | G1 | P2 | +  | -  | 1.70 |
| 178 | P5 | G2 | P2 | +  | -  | 1.79 |
| 179 | P5 | A3 | P2 | +  | +  | 2.81 |
| 180 | P5 | G3 | P2 | +  | -  | 2.28 |
| 181 | P5 | G1 | P3 | -  | -  | 0.53 |
| 182 | P5 | G2 | P3 | -  | -  | 0.62 |
| 183 | P5 | A3 | P3 | -  | -  | 1.63 |
| 184 | P5 | G3 | P3 | -  | -  | 1.11 |
| 185 | P5 | G1 | P4 | -  | -  | 1.17 |
| 186 | P5 | G2 | P4 | +  | -  | 1.26 |
| 187 | P5 | A3 | P4 | -  | +  | 2.28 |
| 188 | P5 | G3 | P4 | +  | -  | 1.75 |
| 189 | P1 | G1 | P6 | -  | -  | 1.32 |
| 190 | P1 | G2 | P6 | -  | -  | 1.41 |
| 191 | P1 | A3 | P6 | -  | -  | 2.43 |
| 192 | P1 | G3 | P6 | -  | -  | 1.90 |
| 193 | P2 | G1 | P6 | -  | -  | 0.73 |

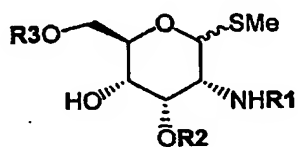


|     |    |    |    |   |   |       |
|-----|----|----|----|---|---|-------|
| 194 | P2 | G2 | P6 | - | - | 0.82  |
| 195 | P2 | A3 | P6 | - | - | 1.84  |
| 196 | P2 | G3 | P6 | - | - | 1.31  |
| 197 | P3 | G1 | P6 | - | - | -0.45 |
| 198 | P3 | G2 | P6 | - | - | -0.35 |
| 199 | P3 | A3 | P6 | - | - | 0.66  |
| 200 | P3 | G3 | P6 | - | - | 0.14  |
| 201 | P4 | G1 | P6 | - | - | 0.20  |
| 202 | P4 | G2 | P6 | + | - | 0.29  |
| 203 | P4 | A3 | P6 | - | + | 1.31  |
| 204 | P4 | G3 | P6 | - | - | 0.78  |
| 205 | P5 | G1 | P6 | - | - | 0.05  |
| 206 | P5 | G2 | P6 | - | - | 0.14  |
| 207 | P5 | A3 | P6 | - | - | 1.15  |
| 208 | P5 | G3 | P6 | - | - | 0.63  |
| 209 | P6 | G1 | P1 | - | - | 1.32  |
| 210 | P6 | G2 | P1 | + | - | 1.41  |
| 211 | P6 | A3 | P1 | - | - | 2.43  |
| 212 | P6 | G1 | P2 | - | - | 0.73  |
| 213 | P6 | G2 | P2 | + | - | 0.82  |
| 214 | P6 | A3 | P2 | - | - | 1.84  |
| 215 | P6 | G3 | P2 | + | - | 1.31  |
| 216 | P6 | G1 | P3 | - | - | -0.45 |
| 217 | P6 | G2 | P3 | - | - | -0.35 |
| 218 | P6 | A3 | P3 | - | - | 0.66  |
| 219 | P6 | G1 | P4 | - | - | 0.20  |
| 220 | P6 | G2 | P4 | - | - | 0.29  |
| 221 | P6 | A3 | P4 | - | - | 1.31  |
| 222 | P6 | G3 | P4 | - | - | 0.78  |

Example Library 3

| Comp. No. | R1 | R2 | R3 | X1 | X2 | X3 | c Log P |
|-----------|----|----|----|----|----|----|---------|
| 223       | N1 | P2 | P7 | -  | -  | -  | 1.49    |
| 224       | N1 | P7 | P2 | -  | -  | -  | 1.49    |
| 225       | N2 | P7 | P3 | -  | -  | -  | 0.38    |
| 226       | N3 | P3 | P2 | -  | -  | -  | 3.11    |
| 227       | N3 | P2 | P3 | -  | -  | -  | 3.11    |

## Example Library 4

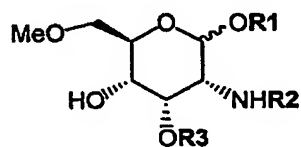


| Comp. No. | R1 | R2 | R3 | X1 | X4 | X2 | c LogP |
|-----------|----|----|----|----|----|----|--------|
| 228       | A1 | P3 | P3 | -  | -  | +  | 0.91   |
| 229       | G1 | P3 | P3 | +  | -  | +  | 0.38   |
| 230       | A2 | P3 | P3 | +  | -  | ++ | 1.00   |
| 231       | G2 | P3 | P3 | ++ | -  | ++ | 0.47   |
| 232       | A3 | P3 | P3 | -  | -  | ++ | 1.49   |
| 233       | G3 | P3 | P3 | +  | -  | ++ | 0.97   |
| 234       | A1 | P3 | P4 | -  | -  | ++ | 1.55   |
| 235       | G1 | P3 | P4 | ++ | -  | +  | 1.03   |
| 236       | A2 | P3 | P4 | -  | -  | +  | 1.64   |
| 237       | G2 | P3 | P4 | +  | -  | +  | 1.12   |
| 238       | A3 | P3 | P4 | +  | -  | ++ | 2.13   |
| 239       | G3 | P3 | P4 | ++ | ND | ++ | 1.61   |
| 240       | A1 | P3 | P1 | -  | -  | ++ | 2.67   |
| 241       | G1 | P3 | P1 | ++ | ND | ++ | 2.15   |
| 242       | A2 | P3 | P1 | +  | -  | +  | 2.76   |
| 243       | G2 | P3 | P1 | ++ | ND | ++ | 2.24   |
| 244       | A3 | P3 | P1 | +  | ND | ++ | 3.25   |
| 245       | G3 | P3 | P1 | ++ | -  | ++ | 2.73   |
| 246       | A1 | P3 | P2 | +  | -  | ++ | 2.08   |
| 247       | G1 | P3 | P2 | ++ | -  | ++ | 1.56   |
| 248       | A2 | P3 | P2 | +  | -  | ++ | 2.17   |
| 249       | G2 | P3 | P2 | ++ | -  | ++ | 1.65   |
| 250       | A3 | P3 | P2 | +  | -  | ++ | 2.67   |
| 251       | G3 | P3 | P2 | ++ | -  | ++ | 2.14   |
| 252       | A1 | P4 | P3 | -  | -  | ++ | 1.55   |
| 253       | G1 | P4 | P3 | +  | -  | ++ | 1.03   |
| 254       | A2 | P4 | P3 | -  | -  | ++ | 1.64   |
| 255       | G2 | P4 | P3 | ++ | -  | ++ | 1.12   |
| 256       | A3 | P4 | P3 | -  | -  | ++ | 2.13   |
| 257       | G3 | P4 | P3 | +  | -  | ++ | 1.61   |
| 258       | A1 | P4 | P4 | -  | -  | ++ | 2.20   |
| 259       | G1 | P4 | P4 | ++ | -  | ++ | 1.67   |
| 260       | A2 | P4 | P4 | +  | -  | ++ | 2.29   |
| 262       | G2 | P4 | P4 | +  | -  | ++ | 1.76   |
| 262       | A3 | P4 | P4 | -  | -  | +  | 2.78   |

|     |    |    |    |    |    |    |      |
|-----|----|----|----|----|----|----|------|
| 263 | G3 | P4 | P4 | +  | -  | ++ | 2.26 |
| 264 | A1 | P4 | P1 | +  | -  | ++ | 3.32 |
| 265 | G1 | P4 | P1 | ++ | -  | ++ | 2.79 |
| 266 | A2 | P4 | P1 | +  | -  | ++ | 3.41 |
| 267 | G2 | P4 | P1 | ++ | -  | ++ | 2.88 |
| 268 | A3 | P4 | P1 | +  | -  | +  | 3.90 |
| 269 | G3 | P4 | P1 | ++ | -  | +  | 3.37 |
| 270 | A1 | P4 | P2 | +  | -  | +  | 2.73 |
| 271 | G1 | P4 | P2 | ++ | -  | +  | 2.20 |
| 272 | A2 | P4 | P2 | ++ | -  | ++ | 2.82 |
| 273 | G2 | P4 | P2 | ++ | -  | ++ | 2.30 |
| 274 | A3 | P4 | P2 | ++ | -  | ++ | 3.31 |
| 275 | G3 | P4 | P2 | ++ | ND | ++ | 2.79 |
| 276 | A1 | P1 | P3 | +  | -  | +  | 2.67 |
| 277 | G1 | P1 | P3 | ++ | -  | +  | 2.15 |
| 278 | A2 | P1 | P3 | -  | -  | ++ | 2.76 |
| 279 | G2 | P1 | P3 | +  | -  | +  | 2.24 |
| 280 | A3 | P1 | P3 | -  | -  | +  | 3.25 |
| 281 | G3 | P1 | P3 | +  | -  | +  | 2.73 |
| 282 | A1 | P1 | P4 | -  | -  | +  | 3.32 |
| 283 | G1 | P1 | P4 | ++ | -  | +  | 2.79 |
| 284 | A2 | P1 | P4 | ++ | -  | ++ | 3.41 |
| 285 | G2 | P1 | P4 | ++ | -  | ++ | 2.88 |
| 286 | A3 | P1 | P4 | -  | -  | +  | 3.90 |
| 287 | G3 | P1 | P4 | ++ | -  | +  | 3.37 |
| 288 | A1 | P1 | P1 | +  | -  | ++ | 4.44 |
| 289 | G1 | P1 | P1 | +  | ND | +  | 3.91 |
| 290 | A2 | P1 | P1 | +  | -  | ++ | 4.53 |
| 291 | G2 | P1 | P1 | +  | -  | +  | 4.00 |
| 292 | A3 | P1 | P1 | +  | -  | +  | 5.02 |
| 293 | G3 | P1 | P1 | -  | ND | ++ | 4.49 |
| 294 | A1 | P1 | P2 | +  | -  | -  | 3.85 |
| 295 | G1 | P1 | P2 | ++ | -  | +  | 3.32 |
| 296 | A2 | P1 | P2 | +  | -  | +  | 3.94 |
| 297 | G2 | P1 | P2 | ++ | -  | +  | 3.41 |
| 298 | A3 | P1 | P2 | +  | -  | ++ | 4.43 |
| 299 | G3 | P1 | P2 | ++ | -  | ++ | 3.91 |
| 300 | A1 | P2 | P3 | +  | -  | +  | 2.08 |
| 301 | G1 | P2 | P3 | ++ | -  | +  | 1.56 |
| 302 | A2 | P2 | P3 | -  | -  | ++ | 2.17 |
| 303 | G2 | P2 | P3 | ++ | -  | ++ | 1.65 |
| 304 | A3 | P2 | P3 | +  | -  | ++ | 2.67 |
| 305 | G3 | P2 | P3 | ++ | -  | ++ | 2.14 |
| 306 | A1 | P2 | P4 | +  | -  | +  | 2.73 |
| 307 | G1 | P2 | P4 | +  | -  | +  | 2.20 |
| 308 | A2 | P2 | P4 | +  | ND | ++ | 2.82 |

|     |    |    |    |    |  |    |      |
|-----|----|----|----|----|--|----|------|
| 309 | G2 | P2 | P4 | ++ |  | ++ | 2.30 |
| 310 | A3 | P2 | P4 | ++ |  | ++ | 3.31 |
| 311 | G3 | P2 | P4 | ++ |  | ++ | 2.79 |
| 312 | A1 | P2 | P1 | ++ |  | ++ | 3.85 |
| 313 | G1 | P2 | P1 | ++ |  | ++ | 3.32 |
| 314 | A2 | P2 | P1 | +  |  | ++ | 3.94 |
| 315 | G2 | P2 | P1 | ++ |  | +  | 3.41 |
| 316 | A3 | P2 | P1 | +  |  | +  | 4.43 |
| 317 | G3 | P2 | P1 | ++ |  | +  | 3.91 |
| 318 | A1 | P2 | P2 | +  |  | ++ | 3.26 |
| 319 | G1 | P2 | P2 | ++ |  | ++ | 2.74 |
| 320 | A2 | P2 | P2 | +  |  | ++ | 3.35 |
| 321 | G2 | P2 | P2 | ++ |  | ++ | 2.83 |
| 322 | A3 | P2 | P2 | +  |  | ++ | 3.84 |
| 323 | G3 | P2 | P2 | ++ |  | ++ | 3.32 |

## Example Library 5



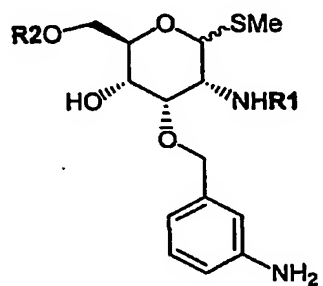
| Comp. No. | R1 | R2 | R3 | X1 | X4 | X2 | c LogP |
|-----------|----|----|----|----|----|----|--------|
| 324       | P3 | A1 | P3 | -  | -  | +  | 0.56   |
| 325       | P2 | A1 | P2 | -  | ND | ++ | 2.91   |
| 326       | P4 | A1 | P1 | +  | -  | +  | 2.97   |
| 327       | P5 | A1 | P3 | -  | -  | +  | 1.05   |
| 328       | P3 | A1 | P4 | -  | -  | ++ | 1.20   |
| 329       | P2 | A1 | P1 | -  | ND | +  | 3.50   |
| 330       | P4 | A1 | P4 | +  | -  | +  | 1.85   |
| 331       | P2 | A1 | P4 | -  | -  | +  | 2.38   |
| 332       | P3 | A1 | P1 | +  | -  | ++ | 2.32   |
| 333       | P5 | A1 | P4 | -  | -  | +  | 1.70   |
| 334       | P2 | A1 | P3 | -  | ND | +  | 1.74   |
| 335       | P5 | A1 | P1 | -  | -  | +  | 2.82   |
| 336       | P3 | A1 | P2 | -  | -  | ++ | 1.74   |
| 337       | P5 | A1 | P2 | +  | ND | +  | 2.23   |
| 338       | P4 | A1 | P3 | -  | -  | -  | 1.20   |
| 339       | P4 | A1 | P2 | +  | -  | +  | 2.38   |
| 340       | P4 | A2 | P2 | +  | -  | ++ | 2.47   |
| 341       | P3 | A2 | P3 | -  | -  | ++ | 0.65   |
| 342       | P3 | A2 | P4 | +  | -  | ++ | 1.30   |
| 343       | P4 | A2 | P4 | +  | -  | ++ | 1.94   |
| 344       | P3 | A2 | P1 | ++ | -  | ++ | 2.42   |
| 345       | P2 | A2 | P3 | -  | -  | ++ | 1.83   |
| 346       | P5 | A2 | P2 | -  | -  | ++ | 2.32   |
| 347       | P3 | A2 | P2 | +  | -  | ++ | 1.83   |
| 348       | P2 | A2 | P2 | -  | ND | ++ | 3.00   |
| 349       | P5 | A2 | P1 | +  | ND | ++ | 2.91   |
| 350       | P4 | A2 | P3 | -  | -  | ++ | 1.30   |
| 351       | P5 | A2 | P4 | ++ | -  | ++ | 1.79   |
| 352       | P2 | A2 | P4 | -  | ND | ++ | 2.47   |
| 353       | P5 | A2 | P3 | -  | -  | ++ | 1.14   |
| 354       | P2 | A2 | P1 | +  | ND | ++ | 3.59   |
| 355       | P4 | A2 | P1 | ++ | -  | ++ | 3.06   |
| 356       | P3 | A3 | P2 | +  | -  | ++ | 2.32   |
| 357       | P5 | A3 | P2 | +  | -  | ++ | 2.81   |
| 358       | P4 | A3 | P3 | -  | -  | ++ | 1.79   |

|     |    |    |    |    |    |    |      |
|-----|----|----|----|----|----|----|------|
| 359 | P2 | A3 | P3 | -  | -  | ++ | 2.32 |
| 360 | P2 | A3 | P4 | -  |    | ++ | 2.96 |
| 361 | P5 | A3 | P3 | -  | ND | ++ | 1.63 |
| 362 | P3 | A3 | P3 | -  | -  | ++ | 1.14 |
| 363 | P4 | A3 | P2 | -  | -  | ++ | 2.96 |
| 364 | P2 | A3 | P2 | -  | ND | ++ | 3.49 |
| 365 | P4 | A3 | P1 | ++ | ND | ++ | 3.55 |
| 366 | P2 | A3 | P1 | +  | ND | ++ | 4.08 |
| 367 | P3 | A3 | P4 | -  | -  | ++ | 1.79 |
| 368 | P4 | A3 | P4 | +  | -  | ++ | 2.43 |
| 369 | P3 | A3 | P1 | ++ | -  | ++ | 2.91 |
| 370 | P5 | A3 | P1 | ++ | ND | ++ | 3.40 |
| 371 | P5 | A3 | P4 | +  | ND | ++ | 2.28 |
| 372 | P4 | G1 | P2 | ++ | -  | ++ | 1.86 |
| 373 | P5 | G1 | P4 | ++ | -  | +  | 1.17 |
| 374 | P2 | G1 | P1 | ++ | ND | +  | 2.98 |
| 375 | P4 | G1 | P1 | ++ | -  | ++ | 2.44 |
| 376 | P2 | G1 | P2 | ++ | ND | ++ | 2.39 |
| 377 | P5 | G1 | P3 | +  | -  | -  | 0.53 |
| 378 | P2 | G1 | P3 | +  | -  | +  | 1.21 |
| 379 | P3 | G1 | P2 | ++ | -  | ++ | 1.21 |
| 380 | P4 | G1 | P4 | ++ | -  | ++ | 1.32 |
| 381 | P4 | G1 | P3 | ++ | -  | ++ | 0.68 |
| 382 | P5 | G1 | P1 | ++ | ND | ++ | 2.29 |
| 383 | P2 | G1 | P4 | ++ | -  | +  | 1.86 |
| 384 | P5 | G1 | P2 | ++ | -  | +  | 1.70 |
| 385 | P3 | G1 | P1 | ++ | -  | ++ | 1.80 |
| 386 | P3 | G1 | P4 | ++ | -  | ++ | 0.68 |
| 387 | P3 | G1 | P3 | +  | -  | +  | 0.04 |
| 388 | P4 | G2 | P3 | +  | -  | ++ | 0.77 |
| 389 | P5 | G2 | P4 | ++ | ND | ++ | 1.26 |
| 390 | P2 | G2 | P2 | ++ | ND | ++ | 2.48 |
| 391 | P5 | G2 | P1 | ++ | ND | ++ | 2.38 |
| 392 | P3 | G2 | P2 | ++ | -  | ++ | 1.30 |
| 393 | P2 | G2 | P3 | +  | -  | ++ | 1.30 |
| 394 | P5 | G2 | P2 | +  | ND | +  | 1.79 |
| 395 | P3 | G2 | P3 | +  | -  | ++ | 0.13 |
| 396 | P4 | G2 | P4 | ++ | -  | ++ | 1.42 |
| 397 | P5 | G2 | P3 | -  | ND | +  | 0.62 |
| 398 | P3 | G2 | P1 | ++ | -  | ++ | 1.89 |
| 399 | P4 | G2 | P1 | ++ | -  | ++ | 2.53 |
| 400 | P2 | G2 | P1 | ++ | ND | ++ | 3.07 |
| 401 | P4 | G2 | P2 | ++ | -  | ++ | 1.95 |
| 402 | P3 | G2 | P4 | ++ | -  | ++ | 0.77 |
| 403 | P2 | G2 | P4 | ++ | ND | ++ | 1.95 |
| 404 | P5 | G3 | P1 | ++ | ND | ++ | 2.87 |

|     |    |    |    |    |    |    |      |
|-----|----|----|----|----|----|----|------|
| 405 | P5 | G3 | P3 | +  | -  | +  | 1.11 |
| 406 | P5 | G3 | P2 | ++ | -  | ++ | 2.28 |
| 407 | P4 | G3 | P2 | ++ | -  | ++ | 2.44 |
| 408 | P2 | G3 | P4 | ++ | ND | ++ | 2.44 |
| 409 | P4 | G3 | P4 | ++ | -  | ++ | 1.91 |
| 410 | P3 | G3 | P4 | ++ | -  | ++ | 1.26 |
| 411 | P3 | G3 | P3 | +  | -  | ++ | 0.62 |
| 412 | P2 | G3 | P3 | -  | -  | ++ | 1.79 |
| 413 | P5 | G3 | P4 | ++ | -  | ++ | 1.75 |
| 414 | P2 | G3 | P1 | ++ | ND | ++ | 3.56 |
| 415 | P3 | G3 | P1 | ++ | -  | ++ | 2.38 |
| 416 | P4 | G3 | P1 | ++ | -  | ++ | 3.03 |
| 417 | P3 | G3 | P2 | ++ | -  | ++ | 1.79 |
| 418 | P4 | G3 | P3 | +  | -  | ++ | 1.26 |
| 419 | P2 | G3 | P2 | ++ | ND | ++ | 2.97 |

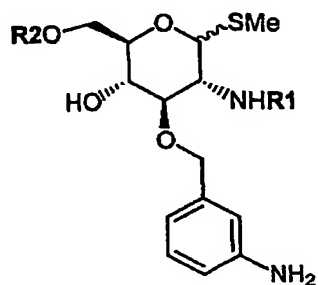


## Example Library 6



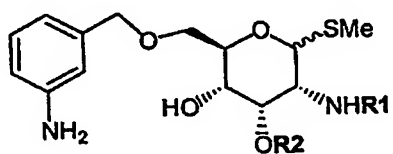
| Object Id | R1 | R2 | X1 | X2 | c LogP |
|-----------|----|----|----|----|--------|
| 420       | E1 | P3 | +  | ++ | 2.98   |
| 421       | E1 | P4 | -  | ++ | 3.61   |
| 422       | E2 | P3 | -  | -  | 2.77   |
| 423       | E2 | P4 | +  | +  | 3.42   |
| 424       | E3 | P3 | -  | -  | 3.05   |
| 425       | E3 | P4 | -  | -  | 3.69   |
| 426       | E4 | P3 | -  | -  | 3.02   |
| 427       | E4 | P4 | -  | -  | 3.67   |
| 428       | E5 | P3 | -  | ++ | 2.83   |
| 429       | E5 | P4 | -  | -  | 3.48   |
| 430       | E6 | P3 | +  | +  | 3.20   |
| 431       | E6 | P4 | -  | -  | 3.84   |

## Example Library 7



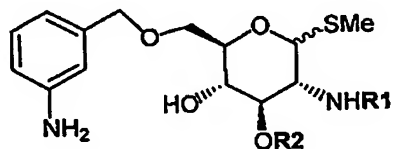
| Comp. No. | R1 | R2 | X1 | X2 | c LogP |
|-----------|----|----|----|----|--------|
| 432       | E1 | P3 | -  | -  | 2.96   |
| 433       | E2 | P3 | -  | -  | 2.77   |
| 434       | E3 | P3 | -  | -  | 3.05   |
| 435       | E4 | P3 | -  | -  | 3.02   |
| 436       | E5 | P3 | -  | ++ | 2.83   |
| 437       | E6 | P3 | +  | -  | 3.20   |
| 438       | E1 | P4 | -  | +  | 3.61   |
| 439       | E2 | P4 | -  | -  | 3.42   |
| 440       | E3 | P4 | -  | -  | 3.69   |
| 441       | E4 | P4 | +  | -  | 3.67   |
| 442       | E5 | P4 | -  | +  | 3.48   |
| 443       | E6 | P4 | +  | -  | 3.84   |

## Example Library 8



| Comp. No. | R1 | R2 | X1 | X2 | c LogP |
|-----------|----|----|----|----|--------|
| 444       | E1 | P3 | -  | +  | 2.96   |
| 445       | E2 | P3 | -  | +  | 2.77   |
| 446       | E3 | P3 | -  | -  | 3.05   |
| 447       | E4 | P3 | +  | -  | 3.02   |
| 448       | E5 | P3 | -  | ++ | 2.83   |
| 449       | E6 | P3 | -  | -  | 3.20   |
| 450       | E1 | P4 | -  | ++ | 3.61   |
| 451       | E2 | P4 | -  | -  | 3.42   |
| 452       | E3 | P4 | -  | -  | 3.69   |
| 453       | E4 | P4 | -  | -  | 3.67   |
| 454       | E5 | P4 | -  | -  | 3.48   |
| 455       | E6 | P4 | ++ | -  | 3.84   |

## Example Library 9



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| Comp. No. | R1 | R2 | X1 | X2 | c LogP |
|-----------|----|----|----|----|--------|
| 456       | E1 | P3 | +  | -  | 2.96   |
| 457       | E2 | P3 | +  | -  | 2.77   |
| 458       | E3 | P3 | +  | -  | 3.05   |
| 459       | E4 | P3 | -  | -  | 3.02   |
| 460       | E5 | P3 | +  | ++ | 2.83   |
| 461       | E6 | P3 | -  | -  | 3.20   |
| 462       | E1 | P4 | ++ | +  | 3.61   |
| 463       | E2 | P4 | +  | -  | 3.42   |
| 464       | E3 | P4 | +  | -  | 3.69   |
| 465       | E4 | P4 | -  | -  | 3.67   |
| 466       | E5 | P4 | +  | -  | 3.48   |

It should be appreciated that various other changes and modifications can be made to any embodiment described without departing from the spirit and scope of the invention.

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Dated this 11<sup>th</sup> day of October 2002

**Alchemia Pty Ltd**

By their Patent Attorneys

**CULLEN & CO.**

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